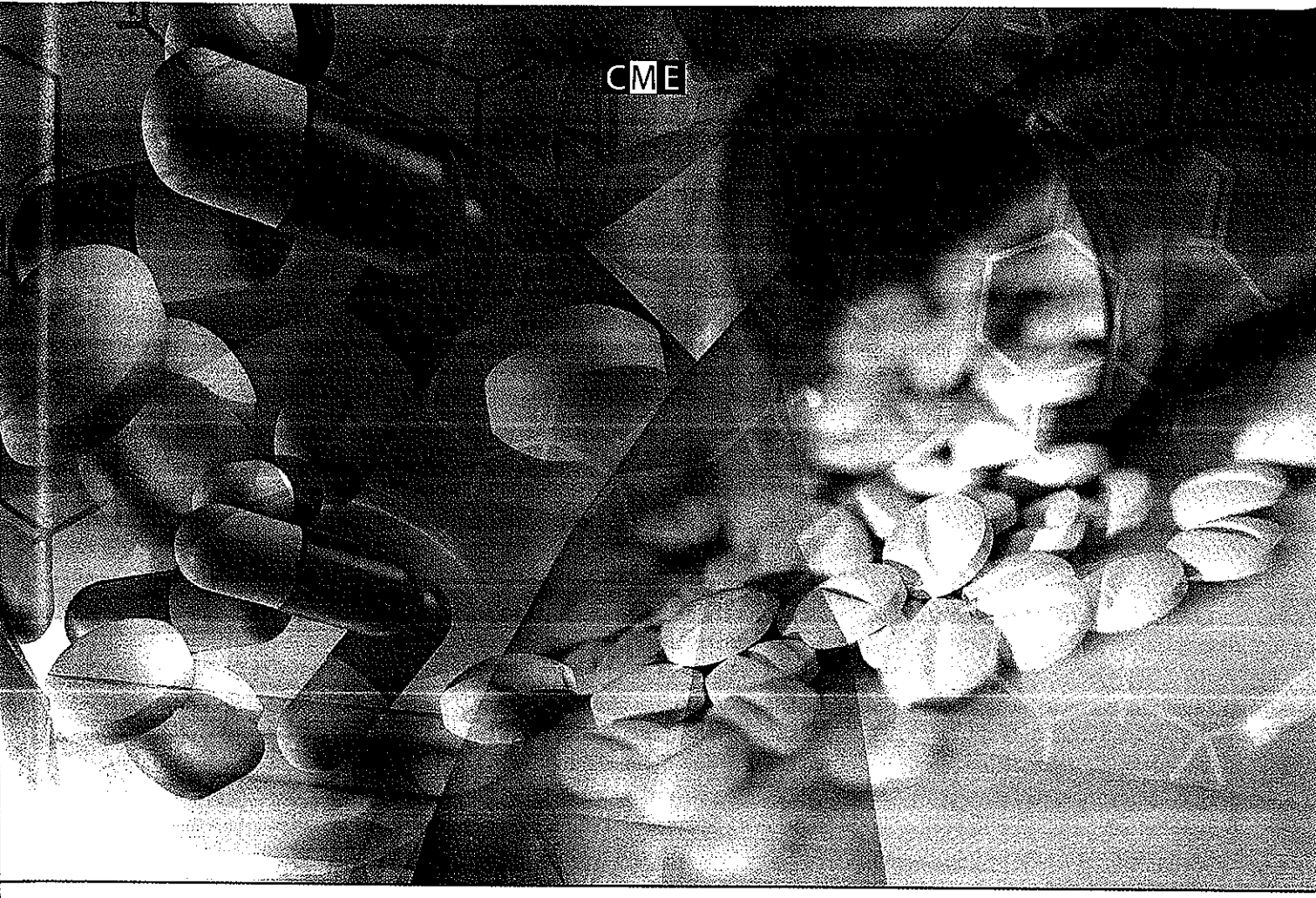
CME



A New Treatment Algorithm for Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is characterized by symptoms of intrusive thoughts and recollections, avoidance of reminders of the trauma, emotional numbing, and hyperarousal. The disorder occurs in approximately 8% of the United States population and follows a chronic course in up to 50%.[1-3] According to the most recent major US epidemiological survey, active PTSD can last more than 20 years.[3,4] Receipt of treatment is associated with an overall shorter course of PTSD.[1]

Existing PTSD treatment guidelines are based on reviews of the extent to which levels of evidence support particular treatments, but they do not address the all-important matter of treatment sequencing, or "what to do next" when the first treatment has failed to bring about remission or good response. Neither do they address the management of PTSD with comorbidities. Six major PTSD treatment guidelines are those published by the Expert Consensus Group,[5] the International Society of Traumatic Stress Studies (ISTSS),[6] the International Consensus Group for Depression and Anxiety,[7,8] the American

Jonathan Davidson, MD; Marcio Bernik, MD, PhD; Kathryn M. Connor, MD; Matthew J. Friedman, MD, PhD; Kenneth O. Jobson, MD; Yoshiharu Kim, MD, PhD; Yves Lecrubier, MD; Hong Ma, MD; Frank Njenga, MD; Dan J. Stein, MD, PhD; and Joseph Zohar, MD

EDUCATIONAL OBJECTIVES

1. Describe the first choice for treatment of posttraumatic stress disorder (PTSD).
2. Discuss the sequencing of treatment for PTSD in the context of level of response.
3. Explain the sequencing of treatment for PTSD in terms of symptomatology.

Psychiatric Association,[8] the US Department of Veterans Affairs and Defense Joint Clinical Practice Guidelines,[9] and the United Kingdom's National Center of Clinical Excellence (NICE).[10]

To address issues of treatment management, for which the levels of evidence typically diminish as one travels down the sequence or considers using drug combinations, there is need to develop treatment algorithms. Accordingly, we present this algorithm for the pharmacologic management of PTSD. At the outset, it is acknowledged that two distinct approaches are of proven benefit in PTSD: the pharmacologic and the psychosocial. Thus, the first choice to be made is whether to offer medication, psychotherapy, or both. Psychosocial treatments, if not used initially, can be added to or replace pharmacotherapy. However, with one exception,[11] we are unaware of any empirical data to support the augmentation of medication with a psychosocial treatment.

In this algorithm, we provide a sequenced approach to the pharmacotherapy of PTSD, taking into account salient symptomatology and diagnostic comorbidity, levels of evidence (LOE; Table 1, see page 889), and extent of response. We also address special issues, including suicidality, comorbidity, ongoing trauma, treatment nonadherence, cultural considerations, issues relevant to women of childbearing potential, legal system involvement, and psychosocial treatment.

The PTSD Algorithm Flowchart and Addendum are essential accompaniments to this article. The flowchart's basic structure is shown in the Figure (see page 890); the full interactive version may be downloaded from http://www.ipap.org/ptsd. The flow chart contains 30 informational nodes; clicking on a given node provides detailed information describing the treatment indications, response, and alternatives. A text file that includes the content of all nodes also is available in PDF format from the Web site. The Addendum is provided on pages 899-900.

A list of the medications discussed in this article, with appropriate dosage ranges,[12] is provided in Table 2 (see page 891).

NODE 1
Diagnosis of PTSD

A range of traumas may precede PTSD (eg, interpersonal violence, motor vehicle accidents, natural disasters), and many are highly prevalent throughout the world. Given data that a significant number of cases of PTSD are underdiagnosed and undertreated, it is important to inquire about exposure to trauma and to maintain a high level of awareness of

Dr. Davidson is director, Anxiety and Traumatic Stress Program, Department of Psychiatry, Duke University School of Medicine, Durham, NC. Dr. Bernik is director, Anxiety Disorders Program, Sao Paulo University, Sao Paulo, Brazil. Dr. Connor is research director, Anxiety and Traumatic Stress Program, Duke University School of Medicine. Dr. Friedman is executive director, National Center for Post-Traumatic Stress Disorder, Veterans Administration Medical Center, White River Junction, VT, and professor of Psychiatry and of Pharmacology, Dartmouth Medical School, Hanover, NH. Dr. Jobson is chairman, International Psychopharmacology Algorithm Project (IPAP), and clinical faculty member, Department of Psychiatry, University of Tennessee, Memphis, TN. Dr. Kim is director, Department of Adult Mental Health, National Institute of Mental Health of Japan, National Center of Neurology and Psychiatry, Tokyo, Japan. Dr. Lecrubier is director of research, French National Institute of Health and Mental Research, Paris, France. Dr. Ma is deputy director, National Center for Mental Health, China Center for Disease Control and Prevention, Beijing, China. Dr. Njenga is chairman, Kenya Psychiatric Association, and president, African Association of Psychiatrists and Allied Professions, Nairobi, Kenya. Dr. Stein is chairman, Department of Psychiatry, Cape Town University School of Medicine, Cape Town, South Africa. Dr. Zohar is director, Israeli PTSD Committee, and professor of psychiatry, Tel Aviv University Medical School, Tel Aviv, Israel.

Address reprint requests to: Jonathan Davidson, MD, Box 3812, Duke University Medical Center, Durham, NC 27710.

Dr. Davidson receives grant/research support from, serves on the Speaker's Bureau for, and serves as a scientific advisor to Pfizer, Solvay, GlaxoSmithKline, Wyeth, and Forest; receives grant/research support from and serves as a scientific advisor to Eli Lilly, Organon, AstraZeneca, Johnson & Johnson, Janssen, Bristol Myers Squibb, and UCB; receives grant/research support from PureWorld, Allergan, Nutrion 21, Cephalon, Parke Davis, Pharmacia, Upjohn, Schwabe, and Merck; and serves as a scientific advisor to Ancile, Roche, MediciNova, Jazz, Novartis, Boehringer Ingelheim, MedTap, Boots, Sanofi-Synthelabo, Alexza, and Brain Cells. Dr. Bernik receives grant/research support from Wyeth and Roche. Dr. Connor receives grant/research support from Eli Lilly, Forest, and GlaxoSmithKline; serves on the Speakers' Bureau for Ortho-McNeil, Pfizer, Wyeth, Cephalon, Predix, and Jazz; serves as a consultant to Ortho-McNeil, Pfizer, Schwarz Pharma, King, Cephalon, Predix, and Jazz; and receives other financial/material support from Schwabe, Nutrition 21, Cephalon, Nordic, Solvay, and Allergan. Dr. Zohar receives grant/research support from Lundbeck and Pfizer and serves as a scientific advisor to Pfizer. Dr. Lecrubier serves as a consultant to Eli Lilly, Sanofi, GlaxoSmithKline, Pfizer, and Pierre Fabre. Dr. Stein receives grant/research support from and/or serves as a consultant to AstraZeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, and Wyeth. Drs. Friedman, Jobson, Kim, Ma, and Njenga have no industry relationships to disclose.

the disorder. Receipt of treatment is associated with an overall shorter course of PTSD (LOE 3).[1]

PTSD is associated with significant morbidity and comorbidity. Recent studies show greater levels of disability, use of welfare, use of prescription medication, and healthcare visits, as well as work impairment, with loss of as many as 4 working days per month.[3,13,14] People with PTSD also demonstrate impaired resilience, exhibiting greater difficulty coping with stress and adversity when compared with the general population, primary care outpatients, and those with depression or other anxiety disorders.[15] Increased rates of attempted suicide have been noted in PTSD, and the adverse physical health consequences related to PTSD are enormous.[16,17] There also is mounting evidence that PTSD is a risk factor for medical illness.[18] Among all anxiety disorders, PTSD was found to be the most costly with, among other things, substantial work loss or cutback.[14]

PTSD is poised to become a major public health problem worldwide.[19] Projections from the World Health Organization suggest that, during the next 20 years, the global burden associated with PTSD will increase dramatically. Road traffic accidents, war-related injuries, and other violence — traumas widely associated with PTSD — are predicted to be among the top 12 causes of disability worldwide.[20]

The particular response to any traumatic event involves multiple factors, including the subjective reaction of the person and consequent symptom severity. Therefore, patients require individual assessment for exposure to trauma and response to the event.

The diagnostic criteria for PTSD, as put forth by the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*),[21] and by the *International Classification for Disease*, 10th edition (*ICD 10*),[22] are presented in Sidebars 1 and 2 (see page 892).

TABLE 1.

Levels of Evidence (LOE)*

1	More than one adequately powered placebo-controlled trial ($n = 30$ per group or greater).
2	One or more small placebo-controlled trials of monotherapy, combination, or augmentation therapy.
3	Case series or open-label trials.
4	Either no published evidence or presence of clinical consensus.

**A number of guidelines already exist for posttraumatic stress disorder, including the Expert Consensus Guidelines,[5] the International Society of Traumatic Stress Studies (ISTSS),[6] the US Departments of Veterans Affairs and Defense joint clinical practice guidelines, 2004,[9] and the United Kingdom's National Institute of Clinical Excellence (NICE).[10] None of these address the matter of clinical treatment sequencing; they are more in the nature of evidence-based reviews in support, or lack thereof, of particular treatments. Our levels of evidence are broadly similar to those of ISTSS and NICE.*

NODE 2
Other Clinical Considerations

At the initial assessment and at intervals during treatment, the clinician should consider other issues relevant to the patient with PTSD (as listed under "Consider at Each Stage" in the Figure). These issues are discussed in more detail in the article by Connor and Stein (see page 902).

NODE 3
SSRI, SNRI, or TCA

Following a diagnosis of PTSD, the recommended first-line pharmacologic intervention is an SSRI (eg, sertraline, paroxetine, fluoxetine), based on strong Level 1 evidence.[23-30] The starting dose can be low (eg, fluoxetine, 10 mg; sertraline, 25 mg; paroxetine, 10mg), reflecting a subset of patients with exaggerated sensitivity to somatic anxiety cues or the doses used in trials (eg, fluoxetine, 20mg.; sertraline, 25 to 50 mg; paroxetine, 20mg). While other drugs in these categories may be beneficial, there is a lack of controlled trials of citalopram[31-32] and fluvoxamine[33,34] (LOE 3) and, to date, no evidence on escitalopram (LOE 4). Paroxetine and sertraline are the only two approved, in some countries, for the treatment of PTSD.

Based on published data, statistically and clinically significant improvement often is seen with the SSRIs by weeks 2 to 4 in the major studies. One study noted a marked improvement in anger/irritability after one week on sertraline,[35] which may be a useful prognosticator of eventual response (LOE 1).[36] An adequate trial requires 6 to 12 weeks, although the early part may be at a subtherapeutic dose while tolerance to side effects is being established. The clinician should expect to see some response after 4 to 6 weeks at an adequate dosage.

Two recent large trials suggest promise for the SNRI venlafaxine. The results are published as of this date only as abstracts.[37,38] Hypertensive and other

To address issues of treatment management, for which the levels of evidence typically diminish as one travels down the sequence or considers using drug combinations, there is need to develop treatment algorithms.

cardiovascular side effects, particularly at high doses, may be a limitation. Small trials of the noradrenergic and specific serotonergic antidepressant (NaSSA) agent mirtazapine (LOE 2, 3)[39,40] also show efficacy in PTSD. However, a study of bupropion (LOE 2) showed no difference between the drug and placebo.[41]

The older antidepressants, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), are of demonstrated efficacy in combat veterans with PTSD (LOE 2).[42,43] In locations where formulary or cost considerations preclude the use of SSRIs or SNRIs, the tricyclics imipramine or amitriptyline may be considered first-line treatments in adults. Aside from two trials of reversible MAOIs with mixed results in civilians and combat veterans (LOE 1),[43,44] the TCA and MAOI drugs have not been studied in controlled trials in civilian samples, in part because of the advent of the SSRIs in recent years. Issues of toxicity also have been a concern with these drugs, in terms of cardiotoxicity, seizure risk, and anticholinergic effects with the TCAs and dietary restrictions and risk of hypertensive crisis with the MAOIs. Considering the levels of evidence in the face of their safety profiles, we do not recommend MAOIs as first-line treatments.

One clear advantage of the antidepressants is their well-established efficacy in treating major depression and other anxiety disorders, which frequently are comorbid with PTSD. However, as noted above, these drugs can be associated with troublesome side effects. For example, common side effects with the SSRIs include nausea, loose stools, headache, insomnia, and agitation with initial treatment, as well as weight gain and sexual dysfunction over the long term.

However, when there is a partial response despite an optimum trial of medication, it may be useful to consider an augmenting agent. At least in depression, even among responders residual symptoms are common and are associated with greater likelihood of relapse. Few controlled studies have compared augmentation strategies with switching medications directly,[46] although both seem effective in around 50% of cases.[47,48] Augmentation offers the advantage of retaining any possible gains from the first agent but the potential disadvantages of polypharmacy (eg, more side effects, drug interactions).[47] The addition of psychotherapy to pharmacotherapy for depression also may be considered in this context.[49,50]

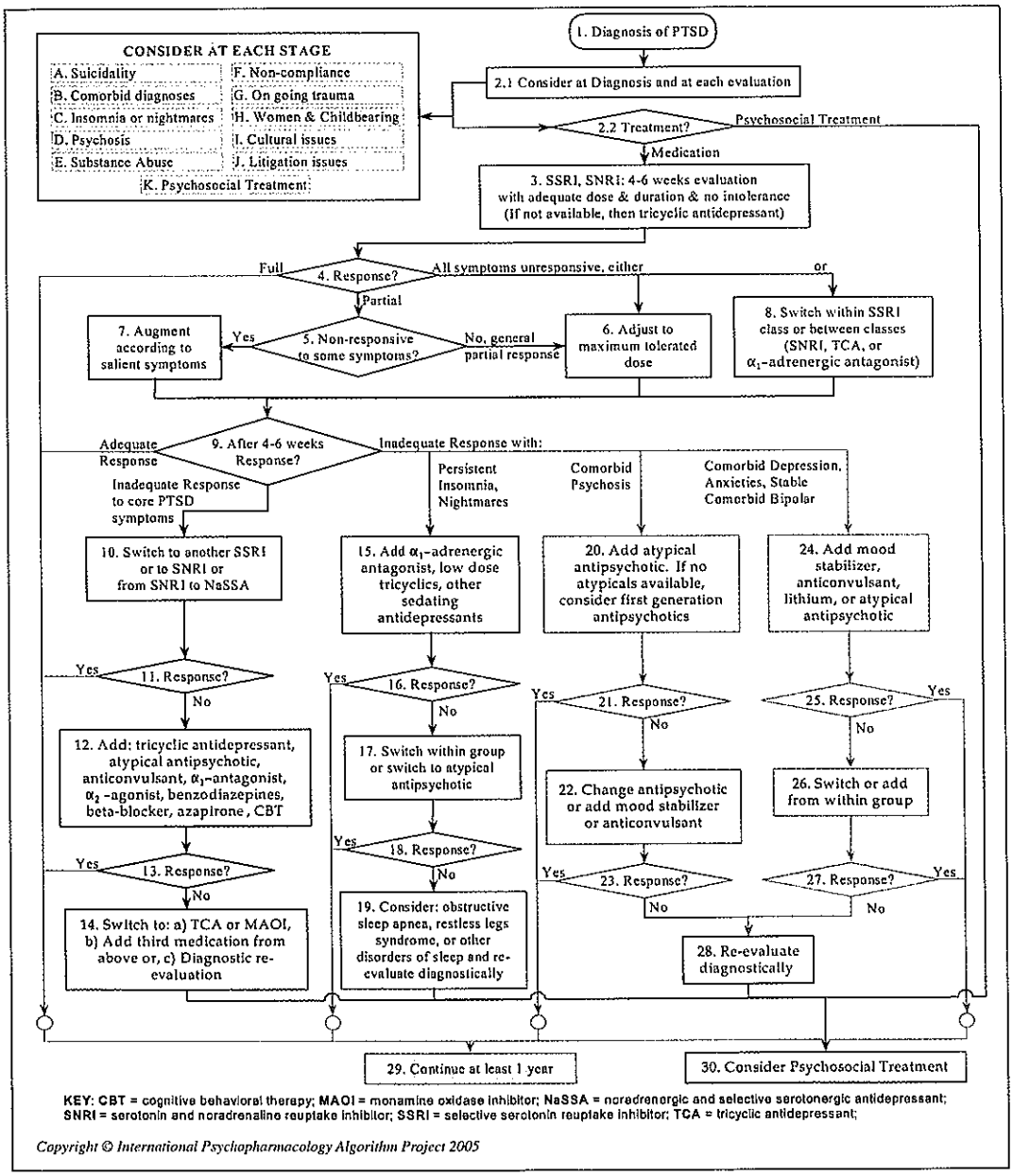


Figure. The basic PTSD treatment algorithm flowchart.

TABLE 2.

Dose Increment Recommendations[12]

Drug	Starting Dose (mg/day)	Maximum Dose (mg/day)	Dose Increments*
Selective serotonin/norepinephrine reuptake inhibitors			
Sertraline	25	200	Increase to 50 mg within a week; subsequently, 25 or 50 mg every 1 to 2 weeks
Paroxetine IR+	10 to 20	50	10 to 20 mg every 2 weeks
Venlafaxine XR	37.5	300	Increase to 75 mg within 1 week; subsequently, 37.5 or 75 mg every 2 weeks
Fluoxetoine+	10	60	10 or 20 mg every 2 weeks
Fluvoxamine+	50	300	50 or 100 mg every 2 to 4 weeks
Citalopram	20	60	20 mg every 2 weeks
Escitalopram	5 or 10	20	5 or 10 mg every 2 weeks
Tricyclic antidepressants			
Amitriptyline+	25 or 50	300	Increase to 50 mg by 1 week; subsequently, 25 or 50 mg every 1 to 2 weeks
Imipramine+	25 or 50	300	Increase to 50 mg by 1 week; subsequently, 25 or 50 mg every 1 to 2 weeks
Other antidepressants			
Mirtzazpine	15	60	15 mg every 2 weeks
Trazodone+	50 or 100	400	Increase to 100 mg after 1 week; subsequently, 50 or 100 mg every 2 weeks
Phenelzine	30	90	Increase to 45 mg after 1 week; subsequently, 15 mg every 2 weeks
Mood stabilizers/anticonvulsants			
Valproic acid/divalproex+	500	2,000	500 mg every 2 weeks according to toxicity or plasma level (where available)
Carbamazepine+	400	1,600	200 mg every 2 weeks and by plasma level (where available)
Lamotrigine	25	400	Increase to 50 mg after 2 weeks; subsequently, 50 mg every 2 weeks (see product label for recommended schedule in the presence of valproic acid or other anticonvulsants)
Topiramate	12.5 or 25	500	25 mg every 2 weeks (or 50 mg at the upper dose ranges)
Atypical antipsychotics			
Olanzapine	2.5 or 5	20	2.5 or 5 mg every 1 to 2 weeks
Risperidone	0.5	3	0.25 or 0.5 every 1 to 2 weeks
Quetiapine	25	300	25 or 50 every 1 to 2 weeks
Adrenergic inhibitors			
Clonidine	0.1	0.6	0.1 or 0.2 mg every 1 to 2 weeks
Guanfacine	1	3	1 mg every 2 weeks
Prazosin	1 to 2		
Propranolol	20 to 40	160	20 to 40 mg every 3 to 4 days

**Dose increments to proceed unless (a) clinical response of at least 50% reduction in symptom severity or (b) problematic side effects. For children and elderly, more cautious dosing is recommended.*
**Generic forms are available.*
Note: Issues of drug–drug interactions are not addressed here but are recognized as clinically important. Levels of evidence to support each drug are available elsewhere. Information in this table is reproduced with permission from the American Psychiatric Association.

NODE 4
Response

Response to treatment after a 12-week trial is described as adequate, partial, or nonresponse. These levels of response are defined as follows:

- Adequate response: at least a 50% improvement in symptoms or a rating of 2 (much improvement) or better on the Clinical Global Impressions of Improvement scale (CGI-I).[51]
- Partial response: 25% to 50% reduction in symptoms.
- Nonresponse: minimal (less than 25%) or no improvement; very little reduction in symptoms.

After 3 to 6 months of treatment or longer, many patients will attain a state of remission, indicated by at least a 70% reduction in symptom severity relative to pretreatment (ie, "70% better") and is

SIDEBAR 1

DSM-IV Diagnostic Criteria for PTSD[21]

A. Traumatic stressor
- An event, or events, in which an individual experiences, witnesses, or is confronted with life endangerment, death, or serious injury or threat to self or others; and
- The individual responds to the experience with feelings of intense fear, horror, or helplessness.

B. Re-experiencing symptoms (one or more)
- Intrusive recollections; distressing dreams; flashbacks; dissociative phenomenon; psychological and physical distress with reminders of the event.

C. Avoidance and numbing symptoms (three or more)
- Avoidance of thoughts, feelings, or conversations associated with the event; avoidance of places, situations, or people that are reminiscent of the event; inability to recall important aspects of the event; diminished interest; estrangement from others; restricted range of affect; sense of a foreshortened future.

D. Hyperarousal symptoms (two or more)
- Sleep disruption; impaired concentration; irritability or anger outbursts; hypervigilance; exaggerated startle reaction

E. Minimum symptom duration of 1 month

F. Symptoms cause distress or functional impairment

Specifiers:

Acute:	Symptom duration from 1 to 3 months
Chronic:	Symptom duration greater than 3 months
Delayed onset:	Symptom onset at least 6 months after the stressor

SIDEBAR 2

ICD-10 Classification of Mental and Behavioral Disorders for PTSD[22]

A. The patient must have been exposed to a stressful event or situation (either short- or long-lasting) of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone.

B. There must be persistent remembering of 'reliving' of the stressor in intrusive 'flashbacks', vivid memories or recurring dreams, or in experiencing distress when exposed to circumstances resembling or associated with the stressor.

C. The patient must exhibit an actual or preferred avoidance of circumstances resembling or associated with the stressor which was not present before exposure to the stressor.

D. Either of the following must be present:

1. Inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor.

2. Persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor), shown by any two of the following:

a. Difficulty in falling or staying asleep.

b. Irritability or outbursts of anger.

c. Difficulty in concentrating.

d. Hypervigilance.

e. Exaggerated startle response.

E. Criteria B, C, and D must all be met within 6 months of the stressful event or of the end of a period of stress. (For some purposes, onset delayed more than 6 months may be included, but this should be specified clearly.)

considered to be the treatment goal for PTSD. Clinical remission would correspond to a CGI-I score of 1.

After 12 weeks of treatment, many patients will experience improvement, with at least a 50% reduction in symptoms. However, further improvement often is noted with continued treatment, with additional improvement in the core PTSD symptoms, disability, and overall functioning. Three studies have demonstrated robust relapse-prevention effects for sertraline[52] and fluoxetine[53,54] when these treatments are continued for 1 year (LOE 1). After 6 months, a 70% reduction in symptoms is expected, representing a state of remission. If symptoms persist and this goal is not attained, refer to subsequent nodes, according to the symptoms present. Because chronic PTSD has a tendency to relapse or deteriorate in as many as 50% of patients if treatment is stopped, we recommend continuation of medication for at least 1 year (LOE 1).

NODE 5
Do Some Symptoms Remain Unresponsive?

At this stage, the clinician is advised to assess whether only certain symptoms remain unresponsive or if all symptoms are still partially nonresponsive. If the former, then augmentation may be appropriate (see Node 7). If the latter, then Node 6 applies. If there is complete nonresponse, then Node 8 applies.

NODE 6
Adjust to Maximum Tolerated Dose

If there is a partial response to an adequate dose of an SSRI (eg, 150 mg sertraline, 40 mg fluoxetine), suggesting that the initial treatment was somewhat helpful but the clinical response was less than adequate, the dose should be titrated to the maximum suggested dose (eg, 200 mg sertraline, 50 mg paroxetine, 60 mg fluoxetine) (Table 2).

NODE 7
Augment According to Salient Symptoms

After 4 to 6 weeks of treatment with an appropriate dose of an SSRI, if there is a partial response, the clinician should assess ongoing symptoms and treat accordingly with augmentation by a second agent. For example, insomnia or nightmares may be treated with prazosin (LOE 2), trazodone (LOE 3), nefazodone (LOE 2),[55] imipramine (LOE 2), or amitriptyline (LOE 2) in low doses. Any of these treatments can benefit not only sleep disturbance but also other aspects of PTSD (LOE 2). Additional information for managing persistent insomnia is given in Node 15. In some instances, while there are no published guidelines, the clinician may choose to increase the dose and augment simultaneously. It is important to establish that symptoms are not due to anxiogenic effects of treatment, however.

Most clinical trials with medication for PTSD have tested the efficacy of monotherapy. Indeed, with the exception of trials with atypical antipsychotics and prazosin, no clinical trials have systematically evaluated the relative effectiveness of different augmentation strategies. Therefore, our recommendations for augmentation strategies for partial responders are extrapolations from monotherapy trials. An alternative option would be to persist at the same (therapeutic) dose, in the expectation that response may eventually occur beyond 12 weeks.

NODE 8
Switch Within SSRI Class or Between Classes

After failure of response (ie, less than 25% improvement) to an SSRI, with core PTSD symptoms persistent after 4 to 6 weeks with an adequate dose, the clinician should switch to another SSRI, SNRI, NaSSA, TCA, or prazosin (an α-1 adrenergic antagonist). An alternative would be to augment the same medication with another pharmacotherapeutic agent, even though there are very limited data on augmentation and none on switching to SNRI/NaSSA or SNRI to NaSSA (all LOE 4). Further, data are not available regarding whether a sequential trial of a second SSRI is as effective as switching to an SNRI or NaSSA after the first unsuccessful SSRI trial. Depending on the severity of the clinical situation, some clinicians may decide to increase the dose and wait longer before switching to another class or augmenting.

One study noted a marked improvement in anger/irritability after one week on sertraline, which may be a useful prognosticator of eventual response.

NODE 9
Response After 6 to 12 Weeks?

If the dosage is already at the maximum and symptoms persist after 6 to 12 weeks, it may be appropriate to introduce a second treatment, while maintaining the initial medication as prescribed. The next course of action will be determined by the presence or absence of specific symptoms and comorbidities, including the persistence of core PTSD symptoms (eg, intrusion, avoidance, numbing, hyperarousal), sleep disturbances, psychotic symptoms, bipolar spectrum disorder, and substance abuse. Sometimes the choice of an augmentation agent may be driven more by clinically significant symptoms, as illustrated by the recommendations for insomnia, psychosis, and substance abuse (Nodes 15, 20, and 24).

Here, the empirical basis for choosing one agent over another is not very solid. Therefore, the following suggestions are based more on clinical lore and known pharmacologic actions. For example, patients exhibiting excessive arousal, hyperreactivity, and, possibly dissociation, might benefit from the addition of an antiadrenergic agent. Patients exhibiting aggressive, impulsive, or labile behavior might benefit from an anticonvulsant or mood stabilizer. Fearful, paranoid, hypervigilant, and psychotic patients might benefit from an atypical antipsychotic. Treatment success (or failure) will be determined by the adequacy of the clinical response and side effects.

NODE 10
Inadequate Response of Core PTSD Symptoms

If there is inadequate response of core PTSD symptoms to 6 to 12 weeks of treatment with a maximum recommended and tolerated dose of an SSRI (eg, 60 mg fluoxetine, 200 mg sertraline; Table 2), the clinician should switch, for example, to another SSRI or to an SNRI, or from an SNRI to an NaSSA, or to a tricyclic drug or prazosin. However, at present, there are no published data on any of these strategies (LOE 4). Further, data are not available as to whether a sequential trial of a second SSRI is as effective as switching to an SNRI or NaSSA after the first unsuccessful SSRI trial.

NODE 11
Response (See Node 4 for definitions)

NODE 12
Augmentation With Medication or CBT

Most clinical trials with medication for PTSD have tested the efficacy of monotherapy with one pharmacologic agent or another. Indeed, with the excep-

tion of trials with atypical antipsychotics, no clinical trials have systematically evaluated the relative effectiveness of different augmentation strategies. Therefore, our recommendations for augmentation strategies for partial responders are extrapolations from monotherapy trials. For example, if a patient fails to respond to an SSRI, we recommend augmentation with an agent that has proven itself as an effective monotherapy or augmentation agent. As a result, our first recommended set of options for augmentation includes TCAs, prazosin, and atypical antipsychotics. Lack of responsiveness to such medications might suggest further augmentation with an agent for which the level of evidence is less strong, such as anticonvulsants, clonidine, guanfacine, or propranolol.

Augmentation offers the advantage of retaining any possible gains from the first agent but the potential disadvantages of polypharmacy. The addition of psychotherapy to pharmacotherapy for depression also may be considered in this context.

Sometimes the choice of an augmentation agent will depend on the presence of comorbid disorders. The presence of comorbid affective or anxiety disorders would suggest use of a medication that is effective for both PTSD and for that disorder (eg, an antidepressant for comorbid PTSD and depression).

Partial response may be managed by augmentation, particularly for aggression, with prazosin (LOE 2), divalproex sodium (LOE 3), risperidone (LOE 2), or lamotrigine (LOE 2), for insomnia/nightmares, or by atypical antipsychotics such as trazodone (LOE 3) risperidone (LOE 2), olanzapine, or quetiapine (LOE 3); buspirone (LOE 3); tiagabine (LOE 4); beta-blockers (LOE 4); or $\alpha 2$ adrenergic agonists (LOE 4) for anxiety/agitation. Benzodiazepines can be used cautiously for panic in patients without substance abuse histories (LOE 4). No data exist as to the effects of benzodiazepines in augmentation treatment, although some data exist suggesting lack of efficacy for monotherapy with alprazolam in chronic PTSD (LOE 2).[56] Nonetheless, on occasion, benzodiazepines may be used adjunctively with other pharmacotherapy (LOE 4). Tiagabine monotherapy was also no different from placebo in one study (LOE 2),[57] but its use in augmentation or for sleep disturbance may be considered (LOE 4). Bupropion appears to be ineffective (LOE 2).[41] Trazodone may be effective (LOE 3),[58] and if all else fails, phenelzine can be considered in certain cases (LOE 2).[43] Addition of cognitive-behavior therapy and prolonged exposure (PE) were found to enhance response in patients who had shown only partial improvement on sertraline (LOE 2).[11]

NODE 13
Response (See Node 4 for definitions)

NODE 14
Switch to TCA or MAOI, Add Third Medication, or Re-evaluate Diagnosis; Consider Psychosocial Treatment

If the patient has failed to achieve an adequate response, there are other options to consider, although data to support all of these recommendations are not available (LOE 4). These include switching to a TCA (LOE 2)[42] or MAOI (LOE 2)[43] or adding a third medication from the list in Node 12. Note that before initiating treatment with an MAOI, attention should be paid to the need for the appropriate medication-free period, if the patient has been receiving another antidepressant.

Efficacy also has been shown for repetitive transcranial magnetic stimulation (rTMS) to the right dorsolateral prefrontal cortex in PTSD (LOE 2).[59]

For psychosocial therapy, see the article by Connor and Stein (page 902).

NODE 15
Inadequate Response With Persistent Insomnia, Nightmares

Sleep disruption characterized by insomnia and nightmares is a core symptom of PTSD. The sleep disturbance or nightmares often persist despite treatment with some SSRI agents and may even be exacerbated by these medications.[35,60] Under such circumstances, we recommend first assessing lifestyle factors, such as over-the-counter medications or heavy caffeine use, that may be contributing to the sleep disturbance. The addition of the $\alpha 1$-adrenergic antagonist prazosin can be quite effective in ameliorating nightmares and insomnia in PTSD (LOE 2, 3).[61,62] Hypotension, syncope, and tachycardia are potential side effects with prazosin; therefore, the patient's predisposition to and risk from hypotension should be considered and blood pressure should be monitored. In addition, it may take some time to build up to a therapeutic dose (4 to 9 mg), and little is known about the metabolism of prazosin or its effects on the cytochrome P450 isoenzyme system.

Other pharmacologic options for which there is considerably less evidence (all LOE 4) but which may be of

benefit include trazodone, low-dose sedating tricyclics, mirtazapine, olanzapine, quetiapine, or zolpidem; tiagabine at night also is an option.[42,63-67] The role of the benzodiazepines here is less clear, and while they may be helpful in reducing hyperarousal symptoms during treatment, they do not appear to confer any additional benefit with respect to the course of PTSD when given in the immediate post-trauma period for acute stress disorder (LOE 2, 3).[68,69]

One nonpharmacologic approach that has shown promise in decreasing nightmares and in improving overall PTSD symptom severity is imagery rehearsal therapy (LOE 1).[70]

NODE 16
Response (See Node 4 for definitions)

NODE 17
Switch Within Group or Switch to Atypical Antipsychotic

If the response remains inadequate, consider switching to another augmenting agent within the same class or to an atypical antipsychotic (LOE 4).

NODE 18
Response (See Node 4 for definitions)

NODE 19
Consider Obstructive Sleep Apnea, Restless Leg Syndrome, or Other Sleep Disorders and Re-evaluate Diagnosis; Consider Psychosocial Therapy

In the event of continued poor response, polysomnography may be indicated to evaluate for suspected sleep-related breathing disorders and periodic limb movement disorders.[71] If obstructive sleep apnea is confirmed, then treatment with continuous positive airway pressure is indicated (LOE 4). If the test does not reveal an obvious cause, an alternative drug may be selected from the above list.

For psychosocial therapy, see the article by Connor and Stein (page 902).

NODE 20
Inadequate Response With Comorbid Psychosis

It is important to distinguish between psychotic symptoms that are part of the PTSD complex versus those that signify a comorbid psychotic disorder. For the former, antiadrenergic, SSRI, and anticonvulsant drugs often are beneficial (LOE 4). Failure to respond would then call for addition of an atypical antipsychotic. Indeed, fearful, paranoid, hypervigilant and psychotic patients might benefit from atypical antipsychotics. If, on the other hand, PTSD is comorbid with a psychotic disorder, then augmentation with atypical antipsychotics should be considered from the beginning.

Psychotic features may be found in as many as 40% of PTSD patients,[72] with commonly reported symptoms including hallucinations, delusions, and paranoid ideation. In many cases, these individuals may not respond adequately to SSRIs. As a result, much of the work done in the area has focused on augmentation of SSRIs with atypical antipsychotics.

The presence of psychotic symptoms that are part of PTSD would call for addition of an atypical neuroleptic, with evidence being limited so far to risperidone (LOE 2), olanzapine (LOE 3), and quetiapine (LOE 3), studies of which appear largely limited to combat veterans,[65,66,73,74] with only one study in civilians.[72] Further, the evidence is mixed, in that some drugs may have not always separated from placebo[76] or have done so only on limited dimensions (eg, psychotic symptoms[74] or sleep and mood[65]).

Inadequate response to the first atypical antipsychotic could be followed by switching to a different medication in the same class. If that fails, then diagnostic re-evaluation is suggested. The specific atypical neuroleptic should be chosen after considering the risk of side effects such as weight gain, aggravation of diabetes, metabolic syndrome, hyperlipidemia, or hyperprolactinemia. Flashbacks, hypervigilance/paranoia, and dissociation can all manifest with psychotic features. For these, antiadrenergics and anticonvulsants are believed to be beneficial (LOE 4).

PTSD remains a very challenging disorder to treat effectively and often requires the use of more than one psychotropic medication, with atypical antipsychotics being used increasingly. Mellman[77] found that 17% of a statewide Medicaid PTSD population had received this form of treatment, a rate which was even higher when depression was also present. There is also growing evidence for efficacy of atypical antipsychotics as adjunctive treatments in PTSD (LOE 3). Thus, it is important to recognize their role in managing the disorder. While the new-generation antipsychotics are less likely to produce extrapyramidal and acute cardiovascular side effects, as compared with the older generation drugs, there is concern about other problems, in particular weight gain, hyperglycemia, hyperlipidemia, diabetes, and long-term cardiac effects via the metabolic syndrome. Careful monitoring is therefore essential, and attention to recently published guidelines on the use of these drugs is recommended.[78]

NODE 21
Response (See Node 4 for definitions)

NODE 22
Change Antipsychotic or Add Mood Stabilizer or Anticonvulsant

If the response remains inadequate, consider switching to another antipsychotic or adding a mood stabilizer or anticonvulsant (LOE 4).

NODE 23
Response (See Node 4 for definitions)

NODE 24
Inadequate Response With Comorbid Depression, Anxiety, or Stable Bipolar Disorder

Comorbid depression, anxiety, and bipolar disorder are found commonly in association with PTSD. Common presentations in bipolar patients with PTSD may include mood lability, irritability, and aggression. In addition, in some instances, antidepressants used to treat PTSD may precipitate hypomania or mania in those predisposed to bipolar disorder. If the symptom picture suggests bipolar spectrum disorder, which also can be associated with PTSD, we recommend addition of either a mood stabilizer or anticonvulsant or an atypical neuroleptic.

Sleep disruption characterized by insomnia and nightmares is a core symptom of PTSD. The sleep disturbance or nightmares often persist despite treatment with some SSRI agents and may even be exacerbated by these medications.

In terms of anticonvulsants and mood stabilizers, divalproex sodium/valproic acid, carbamazepine, topiramate or lamotrigine have been reported as efficacious in PTSD without comorbid bipolar features,[7,58,79-83] again largely in combat veteran populations. There is no evidence (LOE 4) for their use in PTSD with comorbid bipolar disorder. Alternatively, we would consider the use of atypical antipsychotics at this stage, even in the absence of supportive literature (LOE 4), given that the drugs separately are of benefit in bipolar disorder and in PTSD when associated with psychosis or mood disorder. Of note, some mood stabilizers and atypical neuroleptics may require periodic laboratory monitoring (eg, blood levels of carbamazepine and valproic acid, and, for certain atypical neuroleptics, fasting lipid profile and fasting blood sugar).

The sequence of treatment will depend upon which syndrome is clinically the most salient. For stabilized bipolar disorder, untreated PTSD will need addressing. Unstable bipolar disorder will need treatment first. For persistent PTSD with severe depression, it also is possible that electroconvulsive therapy may have value (LOE 4).

For persistent PTSD with other anxiety disorders, we recommend augmentation with treatments of proven or suggested efficacy in the specific disorder. Examples include hydroxyzine, buspirone, trazodone, or benzodiazepines for generalized anxiety disorder (LOE 4); clonazepam, olanzapine, or levetiracetam for social anxiety disorder (LOE 4); and clomipramine or atypical antipsychotics for obsessive-compulsive disorder (LOE 4).

NODE 25
Response (See Node 4 for definitions)

NODE 26
Switch or Add from Within Group

If the response remains inadequate, consider switching to another drug within this group or to adding another drug within this group (see Node 24; LOE 4).

NODE 27
Response (See Node 4 for definitions)

NODE 28
Re-evaluate Diagnosis; Consider Psychosocial Therapy

If response remains inadequate, consider diagnostic re-evaluation.

For psychosocial therapy, see the article by Connor and Stein (page 902).

NODE 29
Continuation for At Least 1 year If Good and Stable Response

NODE 30
Psychosocial Treatment May be Considered at Any Time

SUMMARY

Treating PTSD requires selecting an appropriate first-line treatment, deciding on length of treatment, and knowing when and how to change to another approach. The algorithm presented in this article provides sequential choices to decide whether to persist longer at the highest tolerated dose, augment with a second agent, or switch to another treatment. There is a need to evaluate levels of response (full, partial, or nonresponse), as well as to decide whether partial response is generalized to all PTSD symptoms or limited to select symptoms. Treatment strategies may then be based on which scenario is present. Issues of comorbidity and diagnostic reevaluation must be considered as well.

REFERENCES

1. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995;52(12):1048-1060.
2. Breslau N, Davis GC, Andreski P, Peterson E. Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Arch Gen Psychiatry*. 1991;48(3):216-222.
3. Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. *J Clin Psychiatry*. 2000;61(Suppl 5):4-12; discussion 13-14.
4. Breslau N, Kessler RC, Chilcoat HD, et al. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. *Arch Gen Psychiatry*. 1998; 55(7):626-632.

5. The expert consensus guideline series. Treatment of Posttraumatic Stress Disorder. The Expert Consensus Panels for PTSD. *J Clin Psychiatry*. 1999;60(Suppl 16):3-76.
6. Foa EB, Keane T, Friedman M. *Effective treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies*. New York, NY: The Guilford Press; 2000.
7. Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on posttraumatic stress disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 2000;61(Suppl 5):60-66.
8. Ursano RJ, Bell C, Eth S, et al.; Work Group on ASD and PTSD; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *Am J Psychiatry*. 2004;161(11 Suppl):3-31.
9. *VA/DoD Clinical Practice Guideline for the Management of Post Traumatic Stress Disorders*. Washington, DC: Department of Veterans Affairs/Department of Defense Clinical Practice Guideline Working Group. December 2003. Office of Quality and Performance publication 10Q-CPG/PTSD-04. Available at: http://www.oqp.med.va.gov/cpg/PTSD/PTSD_GOL.htm. Accessed September 30, 2005.
10. *Post-traumatic Stress Disorder: The Management of PTSD in Adults and Children in Primary and Secondary Care*. London, England; Gaskell; 2005. National Institute of Clinical Excellence Clinical Guideline 26. Available at: http://www.nice.org.uk/pdf/CG026fullguideline.pdf. Accessed September 30, 2005.
11. Rothbaum BO, Foa EB, Davidson JRT, et al. Augmentation of sertraline with prolonged exposure in PTSD. Poster presented at: 159th Annual Meeting of the American Psychiatric Association; May 1-6, 2004; New York, NY.
12. Connor KM, Butterfield MI. Posttraumatic stress disorder. *Focus: The Journal of Lifelong Learning in Psychiatry*. 2003;1(3):247-262.
13. Amaya-Jackson L, Davidson JRT, Hughes DC, et al. Functional impairment and utilization of services associated with posttraumatic stress in the community. *J Traumatic Stress*. 1999;12(4):709-723.
14. Greenberg PE, Sisitsky T, Kessler RC, et al. The economic burden of anxiety disorders in the 1990s. *J Clin Psychiatry*. 1999;60(7):427-435.
15. Connor KM, Davidson JRT. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety*. 2003;18(2):76-82.
16. Davidson JRT, Hughes D, Blazer DG, George LK. Post-traumatic stress disorder in the community: an epidemiological study. *Psychol Med*. 1991;21(3):713-721.
17. Boscarino JA. Diseases among men 20 years after exposure to severe stress: implications for clinical research and medical care. *Psychosom Med*. 1997;59(6):605-614.
18. Schnurr PP, Green BL. Understanding relationships among trauma, post-traumatic stress disorder, and health outcomes. *Adv Mind Body Med*. 2004;20(1):18-29.
19. Davidson JRT. Recognition and treatment of posttraumatic stress disorder. *JAMA*. 2001;286(5):584-588.
20. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349(9064):1498-1504.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Publishing; 1994.
22. *The International Statistical Classification of Diseases and Related Health Problems*. 10th ed. Geneva, Switzerland: World Health Organization; 1992.
23. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2000;283(14):1837-1844.
24. Davidson JRT, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry*. 2001;58(5):485-492.
25. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry*. 2001;158(12):1982-1988.
26. Tucker P, Zaninelli R, Yehuda R, et al. Paroxetine in the treatment of posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62(11):860-868.
27. Stein DJ, Davidson JRT, Seedat S, Beebe K. Paroxetine in the treatment of posttraumatic stress disorder: pooled analysis of placebo-controlled studies. *Exp Opin Pharmacother*. 2003; 4(10):1829-1838.
28. Connor KM, Sutherland SM, Tupler LA, Malik ML, Davidson JR. Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. *Br J Psychiatry*. 1999 Jul; 175:17-22.
29. Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC. Fluoxetine versus placebo in posttraumatic stress disorder. *J Clin Psychiatry*. 2002;63(3):199-206.
30. van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in posttraumatic stress disorder. *J Clin Psychiatry*. 1994;55(12):517-522.
31. Seedat S, Lockhat R, Kaminer D, et al. An open trial of citalopram in adolescents with post-traumatic stress disorder. *Int Clin Psychopharmacol*. 2001;16(1):21-25.
32. Seedat S, Stein DJ, Emsley RA. Open trial of citalopram in adults with post-traumatic stress disorder. *Int J Neuropsychopharmacol*. 2000;3(2):135-140.
33. Davidson JR, Weisler RH, Malik M, Tupler LA. Fluvoxamine in civilians with posttraumatic stress disorder. *J Clin Psychopharmacol*. 1998;18(1):93-95.
34. Escalona R, Canive JM, Calais LA, Davidson JR. Fluvoxamine treatment in veterans with combat-related post-traumatic stress disorder. *Depress Anxiety*. 2002;15(1):29-33.
35. Davidson JRT, Landerman LR, Farfel GM, Clary CM. Characterizing the effects of sertraline in post-traumatic stress disorder. *Psychol Med*. 2002;32(4):661-670.
36. Davidson JRT, Landerman LR, Clary CM. Improvement of anger at week one predicts the effects of sertraline and placebo in PTSD. *J Psychiatr Res*. 2004;38(5):497-502.
37. Davidson JRT, Lipschitz A, Musgnung J. Treatment of PTSD with venlafaxine XR, sertraline, or placebo: a double-blind comparison. *Int J Neuropsychopharmacol*. 2004;7(1):P02.228.
38. Davidson JRT, Baldwin D, Stein D, et al. Venlafaxine-XR in the treatment of posttraumatic stress disorder: a 6-month placebo-controlled study. *Neuropsychopharmacol*. 2004;29(Suppl):S97.
39. Connor KM, Davidson JRT, Weisler RH, Ahearn E. A pilot study of mirtazapine in posttraumatic stress disorder. *Int Clin Psychopharmacol*. 1999;14(1):29-31.
40. Davidson JRT, Weisler RH, Butterfield MI, et al. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. *Biol Psychiatry*. 2003;53(2):188-191.
41. Davis LL, Nevels S, Nevels C, et al. Wellbutrin for the treatment of posttraumatic stress disorder. Presented at: 39th Annual Meeting of the New Clinical Drug Evaluation Unit Program; June 1-4, 1999; Boca Raton, FL.
42. Davidson JRT, Kudler HS, Smith RD, et al. Treatment of posttraumatic stress disorder with amitriptyline and placebo. *Arch Gen Psychiatry*. 1990;47(3):259-266.
43. Kosten TR, Frank J, Dan E, et al. Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. *J Nerv Ment Dis*. 1991;179(6):366-370.
44. Baker DG, Diamond BI, Gillette G, et al. A double-blind, randomized, placebo-controlled, multi-center study of brofaromine in the treatment of post-traumatic stress disorder. *Psychopharmacology (Berl)*. 1995;122(4):386-389.
45. Katz RJ, Lott MH, Arbus P, et al. Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic. *Anxiety*. 1994-1995;1(4):169-174.
46. Nelson JC. Treatment of antidepressant nonresponders: augmentation or switch? *J Clin Psychiatry*. 1998;59(Suppl 15):35-41.
47. Fava M. Augmentation and combination strategies in treatment-resistant depression. *J Clin Psychiatry*. 2001;62(Suppl 18):4-11.
48. Marangell LB. Switching antidepressants for treatment-resistant major depression. *J Clin Psychiatry*. 2001;62(Suppl 18):12-17.
49. Thase ME. Psychotherapy of refractory depres-

sions. *Depress Anxiety*. 1997;5(4):190-201.
50. McPherson S, Cairns P, Carlyle J, et al. The effectiveness of psychological treatments for treatment-resistant depression: a systematic review. *Acta Psychiatr Scand*. 2005;111(5):331-340.
51. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: National Institute of Mental Health; 1976:218-222. US Department of Health, Education and Welfare publication (ADM) 76-388.
52. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158(12):1974-1981.
53. Martenyi F, Brown EB, Zhang H, Koke SC, Prakash A. Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. *Br J Psychiatry*. 2002 Oct;181:315-320.
54. Davidson JRT, Connor KM, Hertzberg MA, et al. Maintenance therapy with fluoxetine in posttraumatic stress disorder: a placebo-controlled discontinuation study. *J Clin Psychopharmacol*. 2005;25(2):166-169.
55. Davis LL, Jewell ME, Ambrose S, et al. A placebo-controlled study of nefazodone for the treatment of chronic posttraumatic stress disorder: a preliminary study. *J Clin Psychopharmacol*. 2004;24(3):291-297.
56. Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *J Clin Psychiatry*. 1990;51(6):236-238.
57. Connor KM, Davidson JRT, Weisler RH, Zhang W, Abraham KC. Tiagabine for posttraumatic stress disoarder. Presented at: 17th European College of Neuropsychopharmacology Congress; October 9-13, 2004; Stockholm, Sweden.
58. Hertzberg MA, Butterfield MI, Feldman ME, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry*. 1999;45(9):1226-1229.
59. Cohen H, Kaplan Z, Kotler M, et al. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2004;161(3):515-524.
60. Meltzer-Brody S, Connor KM, Churchill E, Davidson JR. Symptom-specific effects of fluoxetine in post-traumatic stress disorder. *Int Clin Psychopharmacol*. 2000;15(4):227-231.
61. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry*. 2003;160(2):371-373.
62. Raskind MA, Thompson C, Petrie EC, et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2002;63(7):565-568.
63. Hertzberg MA, Feldman ME, Beckham JC, Davidson JR. Trial of trazodone for post-traumatic stress disorder using a multiple baseline group design. *J Clin Psychopharmacology*. 1996;16(4):294-298.
64. Taylor FB. Tiagabine for posttraumatic stress disorder: a case series of 7 women. *J Clin Psychiatry*. 2003;64(12):1421-1425.
65. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002;159(10):1777-1779.
66. Hamner MB, Deitsch SE, Brodrick PS, Ulmer HG, Lorberbaum JP. Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. *J Clin Psychopharmacol*. 2003;23(1):15-20.
67. Dieperink ME, Drogemuller L. Zolpidem for insomnia related to PTSD. *Psychiatr Serv*. 1999;50(3):421.
68. Mellman TA, Bustamante V, David D, Fins AI. Hypnotic medication in the aftermath of trauma. *J Clin Psychiatry*. 2002;63(12):1183-1184.
69. Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. *J Clin Psychiatry*. 1996;57(9):390-394.
70. Krakow B, Hollifield M, Johnston L, et al. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2001;286(5):537-545.
71. Krakow B, Melendrez D, Pedersen B, et al. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. *Biol Psychiatry*. 2001;49(11):948-953.
72. Hamner MB, Frueh BC, Ulmer HG, Arana GW. Psychotic features and illness severity in combat veterans with chronic posttraumatic stress disorder. *Biol Psychiatry*. 1999;45(7):846-852.
73. Monnelly EP, Ciraulo DA, Knapp C, Keane T. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. *J Clin Psychopharmacology*. 2003;23(2):193-196.
74. Hamner MB, Faldowski RA, Ulmer HG, et al. Adjunctive risperidone treatment in posttraumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. *Int Clin Psychopharmacol*. 2003;18(1):1-8.
75. Reich DB, Winternitz S, Hennen J, Watts T, Stanculescu C. A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. *J Clin Psychiatry*. 2004; 65(12):1601-1606.
76. Butterfield MI, Becker ME, Connor KM, et al. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. *Int Clin Psychopharmacol*. 2001;16(4):197-203.
77. Mellman TA, Clark RE, Peacock WJ. Prescribing patterns for patients with posttraumatic stress disorder. *Psychiatr Serv*. 2003;54(12):1618-1621.
78. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *J Clin Psychiatry*. 2004;65(2):267-272.
79. Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry*. 1991;52(9):351-364.
80. Clark RD, Canive JM, Calais LA, Qualls CR, Tuason VB. Divalproex in posttraumatic stress disorder: an open-label clinical trial. *J Trauma Stress*. 1999;12(2):395-401.
81. Lipper S, Davidson JRT, Grady TA, et al. Preliminary study of carbamazepine in posttraumatic stress disorder. *Psychosomatics*. 1986;27(12):849-854.
82. Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry*. 2004;4(1):24.
83. Berlant J, van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry*. 2002;63(1):15-20.
84. Londborg PD, Hegel MT, Goldstein S, et al. Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. *J Clin Psychiatry*. 2001;62(5):325-331.
85. Davidson JRT. Surviving disaster: what comes after the trauma? *Br J Psychiatry*. 2002 Nov;181:366-368.
86. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *J Consult Clin Psychol*. 2000;68(5):748-766.

International Psychopharmacology Algorithm Project PTSD Algorithm

GENERAL PRINCIPLES

I. Initial and Repeated Evaluations (Sidebar 2)

A. PTSD is common and often goes undiagnosed. Given the high prevalence of exposure to trauma (including domestic violence), a trauma exposure history is important.

B. The initial evaluation should use *DSM-IV* or *ICD-10* criteria. Given that most research on PTSD in general, and on pharmacotherapy in particular, has used *DSM-IV* criteria, these may be especially useful.

C. The initial evaluation should include a thorough psychiatric assessment, medical history, and, when appropriate, referral for laboratory or medical evaluation.

D. Initially and repeatedly (at any time of inadequate responses), consider ongoing trauma, key symptoms associated with PTSD that change management (eg, suicide risk, psychotic symptoms, insomnia, nightmares), comorbid psychiatric illness (eg, depression, bipolar disorder, other anxiety disorders, substance abuse), other possible diagnoses, treatment nonadherence, and litigation issues.

E. Patients with bipolar disorder should be stabilized before introducing an antidepressant for PTSD. Similarly, other comorbid disorders (eg, psychotic disorders) may need to be addressed first before treatment for PTSD is begun. In other cases, however, the treatment for PTSD may also be effective for the comorbid disorder and can be begun at the same time.

F. Standardized symptom rating scales are useful tools for baseline and later assessment.

II. Choice of Treatment: Medication, Psychosocial, or Both

A. Initial treatment can be either pharmacotherapy or psychotherapy. Patient preference or special skills of the clinician should influence this choice. Comorbidity may influence the type of medication or psychotherapy prescribed and may also influence the choice of whether to use medication versus psychotherapy.

B. Both approaches have been shown to be efficacious, and each has certain advantages and disadvantages.

III. Acute Stress Disorder Versus PTSD

In the immediate aftermath of a traumatic event, the vast majority of the population will exhibit significant distress. For most, such symptoms will subside within the first 4 weeks, and often within the first 10 to 14 days. Therefore, pharmacologic (or psychosocial) treatment generally should be withheld from all but the most symptomatic and incapacitated people within this period. Supportive measures and psychological first aid are the treatments of choice for such distress during the immediate posttraumatic aftermath.

A. Treatment of chronic PTSD is better understood than is treatment of acute stress disorder or acute PTSD.

B. While many clinicians are likely to believe that the same types of treatment benefit acute stress disorder and acute PTSD (ie, less than 3 months), there are very few studies of treatment in these conditions. With respect to acute stress disorder, there is good evidence that cognitive-behavior therapy is effective for both symptom amelioration and prevention of the later onset of PTSD. Only a few preliminary studies on pharmacological interventions for acute stress disorder have been done. With respect to acute PTSD, there is no reason to delay treatment for people who meet diagnostic criteria.

IV. Medications and Adequacy of Response (Sidebar 1)

A. Patients with PTSD who are going to be treated with medication should, with few exceptions, be prescribed an SSRI or SNRI as their first medication.

B. The response time for treatment of PTSD with an SSRI is generally 4 to 12 weeks. One expects at least a partial response by 4 to 6 weeks with adequate dosage. It is assumed that an adequate or maximally tolerated dose will have been given throughout this recommended period or time. In our present state of knowledge, we cannot say whether it is better to increase the dose, augment, or switch when there has been insufficient

response. Clinicians may wish to keep their options open as to their preferred approaches. It is also the case that response can take longer than 12 weeks, as was noted for a cohort of subjects treated with sertraline, in whom 55% of partial responders at 12 weeks had converted to full responders by 35 weeks.[84]

C. Some patients may demonstrate an initial worsening when starting treatment. In some cases this may be due to activating/anxiogenic effects of the SSRIs. In other instances, it may be related to discussion of the trauma and uncovering previously unaddressed feelings and thoughts associated with the trauma.

D. The patient who has an excellent response to the SSRI should generally be treated for a minimum of 1 year.

E. Benzodiazepines are not recommended as monotherapy and can be harmful in the first few months after trauma. Because a number of antidepressants have been shown to be effective for generalized anxiety and panic, they should be considered before prescribing benzodiazepines. Furthermore, there are no published studies demonstrating efficacy of benzodiazepines in PTSD. If a clinician chooses to prescribe these medications as augmentation for residual comorbid anxiety (eg, generalized anxiety disorder, panic), they should be used as adjuvants only when there is not a history of substance abuse.

F. At each point of evaluating nonresponse, we recommend diagnostic re-assessment, as well as checking for treatment nonadherence.

V. Managing Side Effects

A. Patients with anxiety disorders, including those with PTSD, often experience greater sensitivity to medication side effects and may need a slower dosage titration than used in other patients, such as in depression.

B. When patients only respond partially or fail to respond, it is important to consider whether the symptom presentation represents an inadequate response to the drug or medication side effects.

C. Metabolic and general cardiovascular side effects can occur from antipsychotic medication, as may be the case for some patients with chronic PTSD who are receiving these drugs. This includes glucose dysregulation leading to type II diabetes or worsening of previously controlled diabetes, weight gain, abdominal adiposity, increased triglycerides, or increased total cholesterol and LDL cholesterol. Appropriate monitoring of the metabolic profile is recommended, in accordance with current recommendations.

D. There is the possibility of untoward drug–drug interactions, for example, those mediated by inhibition or induction of the cytochrome P450 enzyme system. With increased rates of comorbid medical illness, there is greater likelihood that a patient with PTSD will be taking other medications. Clinicians are therefore encouraged to become familiar with the more important interactions as they apply to the medications prescribed to treat PTSD.

VI. Social Support

A. Social support is considerably reduced in PTSD,[16] and attention should be paid to this as an important element in the recovery process.[85] Brewin et al.[86] have noted lack of social support to be the single most important predictor of risk for developing PTSD after trauma.

VII. Placebo response

A. Sometimes an initial rapid response that fades may be indicative of a "placebo" or "nonspecific" response, as has been suggested in the depression literature. We do not know to what extent this is the case for PTSD, or how it would be best managed. Some hold that under these circumstances, a medication switch would be preferable to augmentation, but there are no data to inform on this issue.

VIII. Cost–benefit considerations

A. Cost is often an important consideration in drug selection. However, cost of medication must be viewed more broadly as part of a cost–benefit equation, as "cheaper" drugs may have more frequent side effects that bring additional cost burdens. Because of the variability in medication costs from one country to another, we do not make any specific recommendations about this issue. Related is the issue of risk–benefit, which should also be a consideration in drug selection.